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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,903	12/08/2004	Catharina Svanborg	bjs-4984-4	7669

23117 7590 07/27/2007
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EXAMINER	
ROOKE, AGNES BEATA	
ART UNIT	**PAPER NUMBER**
1656	

MAIL DATE	DELIVERY MODE
07/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,903	SVANBORG ET AL.	
	Examiner	Art Unit	
	Agnes B. Rooke	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 18-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 18-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This non-final office action is in response to the paper filed on 5/14/2007. The amendments to the claims filed on 5/14/2007 have been acknowledged.

Status of Claims

Claims 1-14 and 18-25. Claims 15-17 are canceled.

Priority

This application is a 371 of PCT/IB03/01293, filed on 03/07/2003, which claims priority to UNITED KINGDOM 0205347.8, filed on 03/07/2002.

Examiner confirms that a certified copy of the foreign priority application has been received and on file since 09/07/2004.

Applicants Remarks in response to the last office action

Applicants presented no arguments in the response filed on 4/23/2007 and the last response filed on 5/14/2007.

Rejections Withdrawn

The Rejection of claims 9, under 35 USC 112, first paragraph, is withdrawn because Applicants provided SEQ ID NO.

The rejections of claims 7, 9, 12, and 15, under 35 USC 112, second paragraph, are withdrawn because Applicants provided SEQ ID NOs in the claims.

Rejections Maintained or New rejections in view of the Amendments

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-14 and 18-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1, 4, 5, and 9, Applicants refer to a "variant and the fragment" interchangeably in the claim, therefore examiner cannot understand the difference between the variant and the fragment that is referred to in the claims. Further, what is the structure of the variant and what is the structure of the fragment? Is the fragment or variant the same or different? Also, what is the structure of the "fragment of either of these" see claim 1, lines 4-5? Therefore, the claim is indefinite and should be re-written for clarity purposes to define properly the variant of the protein and the fragment of the protein. All dependent claims are included in this rejection because they depend from rejected independent claim and do not cure the deficiency of the independent claim.

In claims 1 and 5, the structure of the "fragment of either of any of these" is not provided therefore the claims are indefinite.

In claims 1and 5, the structure of "the variant and the fragment are at least 100 amino acids in length" is not provided. Therefore the claims are indefinite.

Claims 2 and 5 depend from independent claim 1, which has a limitation that claims a cofactor "that is other than C18:1:9 cis fatty acid." However, claims 2 and 5

claim cofactor "cis C18:1:9 fatty acid" that is excluded from claim 1, therefore the claims lack proper antecedent basis to claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 and 18-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In claims 1 and 5, the structure of the "fragment of either of any of these" is not provided, therefore the claims do not satisfy the written description requirement. The structure of these fragments is not disclosed and thus cannot be ascertained, and thus the structure of these fragments do not correspond with their function. Also, in claims 1and 5, the structure of "the variant and the fragment are at least 100 amino acids in length" is not provided. Therefore the structure of the 100 amino acids does not correspond with its function. Claims 2-4, 6-8, 11-14 are included in this rejection because they depend from rejected independent claim 1 and do not cure the deficiency.

In claim 4, the structure of the "variant or the fragment" is not provided. Therefore, the structure of the variant or the fragment does not correspond with its function.

In claims 9 and 10, the structure of the variant is unknown, thus the structure of the variant does not correspond with its function.

Claim 18 refers to an "unsaturated cis fatty acid." The claim is very broad, since no example of such fatty acid is presented in the claim. Therefore, the structure of claimed fatty acids do not correspond with their function.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 9, 13-14, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Swensson et al., Conversion of α-lactalbumin to α-lactalbumin a protein inducing apoptosis, PNAS (April 11, 2000), vol.97, no.8, p. 4221-4226.

Swensson et al. on pages 4223-4, teach that the conversion of α-lactalbumin to the apoptosis-inducing form involved a cofactor from casein; where α-lactalbumin was converted from the regular, native state to a folding variant with altered biological function, where conversion to HAMLET (human α-lactalbumin made lethal to tumor cells) required partial unfolding of the protein and a specific fatty acid, C18:1, as a

necessary cofactor (instant claims 1, 2, 3, 5, 9, and 19; claim 1 is included in this rejection because Applicants refer to human lactalbumin that is known in the art or claim fragments of lactalbumin or a variant thereof; claim 9 is included in this rejection because it refers to undefined variant of lactalbumin). See pages 4223-4; Figures 1-3 and Abstract. Also, on page 4225, *Discussion* section, the conformation of HAMLET was achieved by changing the conformation of α-lactalbumin from the native to a partially unfolded state by using EDTA treatment because it releases the calcium ions (instant claims 1-6 and 13). (This reference would apply to claims 1-6 of the instant invention, because C18:1 fatty acid could be represented by C18:1:11 or C18:1:9).

α-lactalbumin from human milk whey and recombinant protein was shown to convert to the active complex only on the C:18:1 fatty acid-preconditioned column and only when applied in the apo form. See page 4224, bottom right paragraph. (Instant claims 1-6 of the instant invention).

Claim 13 is included in this rejection because it states that the complex further comprises calcium atoms. Swensson et al. state that the binding of calcium is reduced or that calcium ions are released from the configuration, but the reference never excludes completely calcium ions that could be present in the complex.

Claim 14 is included in this rejection because a pharmaceutically acceptable carrier could be water or a buffer solution, for example.

Claims 1-5, 14, 14, 18, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Hakansson et al., A folding variant of α-latalbumin with bactericidal

activity against Streptococcus pneumoniae, Molecular Biology, 2000, 35(3), pages 589-600.

Hakansson et al. teach α-latalbumin folding variant where the native α-latalbumin could be converted to the active form in the presence of cofactor C18:1 fatty acid. See Abstract. On page 562, Table 2, shows protein folding variants of α-latalbumin where different fatty acids were used: oleic acid (C18:1), stearic acid (C18:0) and palmitic acid (C16:0). (Instant claims 1-5, 13, 14, 18, 19).

On page 595, left paragraph, it is taught that α-latalbumin from human milk whey was activated by cofactor as a C18:1 fatty acid. (instant claims 1, 2, 3, 5, 6, and 18)

On pages 595, right column, and page 596, left column, it is taught that the well known native form of α-latalbumin has affinity to calcium, where the calcium binding cite is co-ordinated by the side chain carboxylates As-82, Asp-87 and Asp 88p; where the calcium ion the molecule changes the conformation to the apo-form.

Therefore, the aforementioned rejected claims are anticipated by Hakansson et al. because the structure α-lactalbumin is known in the art and a complex of the lactalbumin and calcium is activated by fatty acids such as C18:1 or others as disclosed by the prior art. Further, Applicants claim a fragment or a variant of albumin (see claim 1).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Swensson et al., Conversion of α-lactalbumin to α-lactalbumin a protein inducing apoptosis, PNAS (April 11, 2000), vol.97, no.8, p. 4221-4226 in view of Permyakov et al., Mutating aspartate in the calcium-binding site of α-latalbumin: effects on the protein stability and cation binding, Protein Engineering, vol.14, No.10, pp. 785-789, 2001.

The teachings of Swensson et al. are disclosed above. Swensson et al. does not teach mutations in α-lactalbumin.

Permyakov et al. teach measurements of Ca(II) affinity of mutants of α-lactalbumin, where mutants D87A and D87Nα-lactalbumin are unable to bind calcium ions. See page 785, middle of the right paragraph. (instant claims 1, 6, 7, 8)

On page 786, recombinant proteins D87A and D87Nalpha-lactalbumin were expressed in E.coli, and as a consequence of protein expression, the recombinant protein contained extra methionine residue on N-terminus, which is known to destabilize α-lactalbumin; and where α-lactalbumin with D87 N mutation was unable to fold properly or bind calcium ions (Claims 7 and 8 of the instant invention).

Therefore, it would have been obvious to one of an ordinary skilled in the art at the time the invention was made to design a mutated α-lactalbumin where calcium binding site has been modified, so that the affinity for calcium is reduced as taught by

Permyakov et al. and combine these with teachings of Swensson et al. that teach a composition of α-lactalbumin and a cofactor with altered calcium binding ability.

Objections to Claims

Claims 1, 10, and 20-25 should be re-written for clarity/grammatical purposes, where in line 2, it states α-lactalbumin at "least 70% identical" should be: "has at least 70% identity," for example.

An additional period from claim 6 should be deleted.

In claim 4, the Applicants claim "a the variant" thus proper correction is required.

In claim 25, the word "is" is missing from line 2.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnes Rooke whose telephone number is 571-272-2055. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-272-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information about the PAIR system, see http://pair-direct.uspto.gov. Should you have

any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

AR

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